Growth Hormone Deficiency (GHD) from Birth to 2 Years of Age: Diagnostic Specifics of GHD during the Early Phase of Life

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Key Words

Fetus · Infant · Growth hormone · Insulin-like growth factor I · Growth hormone deficiency · Hypothalamic-pituitary axis · Insulin-like growth factor binding protein

Abstract

The first 2 years of life represent a transition period when growth changes from predominantly growth hormone (GH) independent to GH dependent. In the fetus, growth is influenced by genetic and environmental factors in addition to nutrition and growth factors including insulin. In infancy, nutrition remains an important determinant of growth. GH levels are high in mid-gestation and at birth, then fall sharply for the first few weeks and more slowly over the next few months reaching pre-pubertal levels by around the age of 6 months. GH deficiency (GHD) may present at birth with hypoglycaemia, micropenis or prolonged conjugated hyperbilirubinaemia. Although length at birth is usually within the normal centile ranges, post-natal growth failure can begin early and be profound.

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Growth Hormone in Fetal and Early Life

Growth hormone (GH) can be detected in the fetal circulation from 10 weeks of gestation [1], and concentrations of GH rise from 12 weeks to a peak in mid-gestation, when levels are higher than at any other time in life (~100 ng/ml), and then fall towards term [2, 3]. Animal studies have demonstrated that fetal GH secretion from the pituitary is pulsatile and under hypothalamic control [4] as well as negative feedback control linked to circulating insulin-like growth factor I (IGF-I) levels [5]. The fall of GH levels in late gestation may be related to rising endogenous IGF-I levels.

At birth, GH levels are high and pulsatile, with elevated baseline, mean and peak levels [6–10]. Pulsatile GH secretion has been described in both term [6–8] and pre-term [6, 8–10] infants, with pre-term babies having higher pulse amplitudes but similar pulse frequency compared with term babies [6]. Estimates of pulse frequency have ranged between 2.5 and 9.9 per 12 h and may be greater in the first 48 h [10]. After the first 2 days of life, there is a decrease in pulse frequency, pulse amplitude and baseline levels [7].

Study of the influence of sleep on GH secretory patterns in the first 2 years of life has been hampered by lack of non-stressful sampling techniques. In older individu-

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als, GH secretion is influenced by sleep-wake cycles, with slow-wave sleep triggering GH release [11, 12]. Within the limitations of the sampling techniques, GH levels are not different between wake and sleep before 3 months of life. After 3 months, GH levels are significantly higher during sleep as a result of much lower levels when awake compared with during the first 3 months [13].

The high GH levels seen during the neonatal period may result from a lack of negative feedback from relatively low levels of circulating IGF-I [5]. The changes over the first few days may represent changes in the pituitary regulation of GH by somatostatin (SMS) and GH-releasing hormone (GHRH). Although both SMS and GHRH are present in the hypothalamus at birth, there are conflicting data regarding whether the pituitary responds to exogenous GHRH in the neonatal period [14, 15]. In the neonatal rat, SMS increasingly inhibits spontaneous and GHRH-stimulated GH release over the first few weeks of life [16].

In the newborn infant, there is a relationship between GH pulsatility, feeds and insulin secretion [9]. A clear post-prandial rise in GH, and the coincident pulses of GH and insulin, suggest that the stimulus for both may be related to feeds. The mechanism is unknown, but it may be associated with a direct effect of insulin, or to other feed-related secretagogues (such as changes in amino acids, or free fatty acids). A paradoxical rise in GH during hyperglycaemia has been observed in the first 6 days of life, and is most pronounced in pre-term infants [17]. It has been suggested that the increase in GH induced by a glucose load could be a signal for protein synthesis.

The role of the elevated levels of GH in the fetus and in infancy is unclear. Although GH receptors are present during fetal life [18], studies in animals [19] and human fetuses [20] suggest that GH does not play a major role in fetal growth. An alternative metabolic role for the high GH levels has been proposed [21, 22]. It may induce insulin resistance and thus protect the fetal brain from hypoglycaemia, whereas the lipolytic effects could provide alternative fuels for metabolism [22].

GH levels in the blood decline quite rapidly over the first 2 weeks of life, although elevated levels compared with older children and adults may still be apparent at 8 weeks of life [1, 21, 23]. The pattern of decline in GH levels over the first 2 years of life is shown in figure 1 [24].

GH-receptor mRNA is present in chondrocytes, osteoblasts, fibroblasts and the epidermis from 15 weeks of gestation [25] and from 30 weeks of gestation it is present in hepatocytes [26]. GH-binding protein (GHBP) levels are

Fig. 1. The pattern of decline in GH levels over the first 2 years of life. Data from Leger et al. [24].

low during fetal life, but are detectable from mid-gestation. Post-natally, GH receptor expression is gradually up-regulated in many tissues [18]. Levels are low in the newborn period with binding levels of around 27% of those of adults [27]. Levels remain low during the first 3 months of life [28] and rise sharply at 6 months [29], rising thereafter to reach double the neonatal level by 6 years of age [27].

Insulin-Like Growth Factors

IGF-I and IGF-II are major mediators of pre- and post-natal growth [30–32]. In the mouse, evidence for the role of IGF-I and IGF-II in growth during fetal and early neonatal life comes from transgenic models incorporating disruption of IGF-I, IGF-II and IGF receptor genes [33, 34]. Disruption of either IGF-I or IGF-II production results in severe growth restriction with a 40% reduction in birth size. Disruption of the IGF-I receptor resulted in greater growth impairment and was uniformly lethal at birth. Animals lacking both the IGF-I and IGF-II receptors had the most severe phenotype (30% normal size). The data suggest that the fetal growth effects of both IGF-I and IGF-II are additive. IGF-I-deficient mice had impaired post-natal growth. In the human, a patient with

Table 1. Causes of the change in the primary function of GH from a probable metabolic role to a growth-promoting role

Maturation of the hypothalamic-pituitary axis
Secretion of IGF-I becoming GH dependent rather than dependent on nutrition and insulin
Emergence of GH receptors mirrored by an increase in GHBP
Change in the pattern of IGFBPs

a homozygous deletion of the *IGF-I* gene had severe in utero growth failure that persisted post-natally, providing direct evidence of a GH-independent role for IGF-I in growth both pre- and post-natally [35].

IGF-I levels increase towards term [36, 37] and levels at birth are correlated with gestational age. Although fetal IGF-I levels are low, they correlate with fetal weight and bone length [38, 39]. At birth, there is a relationship between IGF-I levels and birth size that is independent of gestation [9, 31, 39–41]. In the fetus, there is evidence that insulin rather than GH mediates IGF-I production [42]. As the major determinant of fetal growth is substrate availability, the growth-retarded ovine fetus has relatively low levels of IGF-I, irrespective of the cause of the intra-uterine growth retardation [42, 43]. Relatively low levels of IGF-I are also found in the growth-retarded human fetus [36, 39]. At birth, the levels of IGF-I are approximately half of those seen in adults. Levels fall by 25% on the first day after birth and return toward birth levels by the end of the first week, but remain low for the first 15–18 months and rise gradually thereafter [44].

Fetal IGF-II levels increase with gestational age [39, 41, 45, 46], although this finding is not consistent [47]. The levels of IGF-II do not correlate with fetal weight or length [38, 39] and the precise role of IGF-II in human growth is unclear.

All six IGF-binding proteins (IGFBP) are widely expressed in fetal tissues [48–51]. The binding proteins modulate IGF action by regulating binding to the type 1 IGF receptor and regulating bioavailability by increasing their half-life. In addition, they regulate tissue distribution and capillary transport.

IGFBP-3 concentrations increase with increasing gestational age [52] with fetal levels being 10–15% of adult levels. IGFBP-3 levels do not change significantly after birth, but rise slowly over the first 2 years of life [24]. Levels are lower in babies who are small for gestational age (SGA) and higher in babies who are large for gestational age compared with normal babies. In contrast, IGFBP-1

and IGFBP-2 are elevated in SGA babies [44]. IGFBP-1 levels in the fetus are inversely correlated with IGF-I levels and are not elevated in the fetus, which may be important for the normal delivery of IGF-I to the tissues. Umbilical cord blood IGFBP-1 levels correlate inversely with birth size [44, 53]. At birth, IGFBP-1 levels have been reported to be high but variable [28, 46], suggesting that IGF-I transport and availability are decreased immediately after birth. This may be important in protecting the newborn from hypoglycaemia. The paradox of low IGF-I levels at a period of maximal human growth may be explained by bioavailability. IGFBP-3 levels in fetal serum are four times lower than in adult serum [52], and the mean molar ratio of [IGF-I] + [IGF-II] to [IGFBP-3] is 50% higher than in adult serum [52, 54]. In contrast, IGFBP-2 levels in the fetus are elevated three-fold [52]. Hence, relatively more IGF will be bound to the lower-affinity IGFBP-2 molecule (compared with IGFBP-3) with a probable increased bioavailability [52]. The high levels of IGFBP-1 decrease over the first month of life [28]. Normative data for IGF-I, IGFBP-2 and IGFBP-3 from birth through childhood have been published, although there are wide variations between studies [55].

The role of insulin in fetal growth has been clearly identified. Body weight at birth is related to the amount of functioning pancreatic tissue, with hyperinsulinaemic babies being macrosomic and SGA babies having reduced amounts of pancreatic tissue [56]. Insulin may augment fetal growth by influencing production of IGF-I and IGF-II [57, 58], as well as direct anabolic and growth-promoting effects. Umbilical venous plasma insulin concentration and fetal insulin:glucose ratio increase exponentially with gestation [59]. There is a positive correlation between birthweight and umbilical vein insulin levels [36]. In addition, both the type 1 IGF receptor and insulin receptor share homology, with both ligands able to bind to both receptors. The role of insulin in post-natal growth is unclear, but although it may remain important, nutrition is still a dominant determinant.

In summary, during the first 2 years of life, there is a change in the primary function of GH from a probable metabolic role to a growth-promoting role. The causes of this change are shown in table 1.

Gene Mutations Resulting in GH Deficiency

Although the majority of cases of GH deficiency (GHD) are idiopathic [60], mutations involving the genes of the hypothalamic-pituitary-GH axis may be causative.

Mutations in the *GHI* gene can be transmitted in an autosomal recessive [61] or dominant [62] manner. Mutations of the GHRH receptor gene may also be inherited recessively [63].

Multiple pituitary hormone deficiencies (MPHD) with a genetic basis may result from pituitary activation factors that are involved in the embryonic development of the anterior pituitary gland. An increasing number of patients with MPHD are found to have mutations within pituitary transcription factors *PIT1*, *PROP1* and *HESX1* [64]. *PIT1* may be inherited dominantly or recessively and is associated with prolactin and thyroid-stimulating hormone (TSH) deficiency, in addition to GHD. Patients with *PROP1* defects may also have absent gonadotropin, and reduced cortisol responses to adrenocorticotrophic hormone (ACTH) occur in a third of patients [64].

Clinical Presentation of GHD during the First 2 Years of Life

GHD may be isolated (IGHD) or associated with MPHD. There is an increased incidence of perinatal problems in children who are later diagnosed with idiopathic GHD, in particular those delivered by breech delivery (occurring in 7–65% of patients with GHD [65–68]), or caesarian section, those experiencing prolonged or precipitous deliveries, intrapartum distress or having low Apgar scores at birth [65, 66, 69–71]. These complications are equally frequent in those who have IGHD compared with MPHD [72, 73]. It is not clear whether these adverse events account for the trauma to the pituitary stalk, or whether a developmental anomaly of the hypothalamic-pituitary axis predisposes the baby to a breech presentation or the other adverse events.

When presenting in neonates, the most frequent symptom of GHD is severe and persisting hypoglycaemia, which may be associated with convulsions [74, 75]. In boys, there may be micropenis. Babies presenting with GHD within the first 24 h are often hypothermic (personal observation). Prolonged, conjugated hyperbilirubinaemia may alert a physician to the diagnosis. There are conflicting data regarding whether neonatal symptoms are more frequent in babies with MPHD than in those with IGHD [72, 73]. Dysmorphic features, particularly mid-line defects or craniofacial anomalies, may alert the clinician to dysfunction of the hypothalamic-pituitary axis.

In a review of 1,600 cases of children who were considered for pituitary GH therapy between 1963 and 1984, 29

(1.8%) presented under 2 years of age. Of these, 16 presented within the first 6 months, five having IGHD and 11 having MPHD. Eleven of these 16 children presented with symptomatic hypoglycaemia, predominantly within the first 24 h of life, and 10 of these had MPHD. Four presented with failure to thrive (poor weight gain, but poor length gain detected on review) and one with excessive weight gain at 5 weeks. Of the children presenting between 6 months and 2 years, two had MPHD and 11 had IGHD. One of the two children with MPHD had a hypoglycaemic convulsion at 6 months and the other was diagnosed with failure to thrive and developmental retardation. Of the children with IGHD, all presented with failure to thrive and five of the six boys had microgenitalia [74].

Although it has been believed that children with congenital GHD were of normal size at birth [76, 77] (and from the observation that babies with anencephaly have a normal birth length), the majority of studies since the 1990s have shown that these children have a birth length and weight below the mean, with some children having very severe growth failure even at birth. As the majority of birthweights and lengths are within the normal centiles, however, in the absence of other symptoms these children rarely present at birth. Mean birth length standard deviation scores (SDS) of children later diagnosed with GHD are reported to be +0.4 [78], –0.87 [65], –0.9 [75], –1.3 and –1.7 (depending on subsequent growth patterns [79]) and –2.1 [66]. Weight SDS was higher than length suggesting a degree of adiposity. Profound growth failure may become apparent within the first few months of life. Some children appear to follow the ‘infancy’ curve of the infancy-childhood-puberty model for the first 6 months of life [79, 80], whereas in other children the growth failure is more immediate [66, 78, 79, 81]. In 46 children with congenital GHD, for example, Pena-Almazan and colleagues demonstrated a fall in length SDS of 1.6 standard deviations (SD) over the first 6 months of life, with a further fall of 0.6 SD over the second 6 months and a total loss in length of 2.2 SD in the first year. Weight changes over this period were a loss of 0.98 SD in the first 6 months and a further loss of 0.3 SD in the second 6 months [78].

Early growth failure is not universal in children with congenital GHD. For example, children with septo-optic dysplasia or defects in *PIT1* or *PROP1*, may appear to grow normally in early life. The reason for this may be that in those with a hypothalamic defect, the relative paucity of somatostatinergic inhibition of GH secretion results in little impact on growth in the first year. In those

with *PROPI* mutations, the onset of the hormone deficiencies may be delayed, with a median age of diagnosis of GHD in patients with *PROPI* mutations being 6–8 years [82]. *PROPI* or *PITI* mutations should be suspected in patients with MPHD particularly when cases are familial, there is consanguinity, or there are reduced pituitary responses to hypothalamic releasing hormones. A molecular diagnosis will aid appropriate hormone replacement strategies and pre-symptomatic diagnosis in other family members.

Diagnosis of GHD

GH levels (as well as cortisol, ACTH, TSH and thyroxine) should be measured at the time of hypoglycaemia in any baby with severe or symptomatic hypoglycaemia for which another cause is not obvious. Levels of less than 20 ng/ml would suggest GHD in the newborn [83]. Careful examination may reveal mid-line defects and cerebral ultrasound examination may detect cerebral anomalies that may be associated with septo-optic dysplasia (e.g. absence of the corpus callosum).

In children with growth failure in whom other causes have been excluded, low IGF-I and IGFBP-3 levels may indicate GHD, particularly if levels are below –2 SD. Elevated IGFBP-2 levels may provide additional information [55]. However, these tests are not diagnostic alone.

GH stimulation tests may be undertaken according to standardized protocols, but insulin tolerance tests are probably not appropriate because clinical signs of severe hypoglycaemia in this age group are not always apparent. Glucagon stimulation tests will also investigate the adrenal axis. Once more, late hypoglycaemia may be profound and should be anticipated, and if this develops, treatment with hydrocortisone in addition to dextrose may be appropriate. Diagnosis of GHD after the neonatal period, when GH levels will have fallen, is made with a GH level of less than 10 ng/ml.

Samples for bone age estimation in children below the age of 1 year are generally taken from the knee and ankle. If the child is over the age of 1 year, the left hand and wrist may be used. In GHD, delay in bone age is typical. In infants presenting with symptoms or signs of MPHD, ophthalmological examination may disclose optic nerve hypoplasia of one or both eyes in children with septo-optic dysplasia.

Magnetic Resonance Imaging

Children diagnosed with GHD during the newborn period have a high incidence of a structural anomaly of the hypothalamic-pituitary region, or septo-optic dysplasia or other brain malformation. In this situation, a magnetic resonance imaging (MRI) scan can aid interpretation of the child's condition. Normally, the anterior pituitary and stalk are well defined, and the posterior pituitary is easily identified as a hyperintense bright spot on unenhanced imaging studies. A small or absent anterior pituitary gland, attenuated or absent pituitary stalk, and an ectopic posterior pituitary gland are all seen in hypopituitarism. In addition, associated cerebral abnormalities including optic nerve hypoplasia, absent septum pellucidum, absent corpus callosum or Chiari I malformation can be identified.

Trauma to the pituitary stalk (e.g. occurring during delivery) will result in a hypoplastic anterior pituitary gland and, with regeneration of the distal axons of the hypothalamus, a superiorly located posterior pituitary gland. Children with congenital GHD whose MRI scans demonstrate pituitary stalk interruption syndrome are likely to have lower GH levels on provocative stimulation, and are more likely to have MPHD, a younger age at diagnosis and neonatal hypoglycaemia [84]. When comparing the scans of children with GHD alone with those of children who have MPHD, children with MPHD are more likely to have a thin, truncated or absent pituitary stalk [85], and an ectopic or absent neurohypophysis, although the position of the posterior pituitary and size of the adenohypophysis is similar between the two groups [73, 85, 86]. When corrected for pubertal status at the time of MRI, one study found that the adenohypophysis was more likely to be small or absent in patients with MPHD [85].

Anterior pituitary size is small or normal in MRI scans in patients with *PITI* mutations. There is no consistent relationship between pituitary size, age of patient or type of mutation [64]. Those with *PROPI* mutations also have small or normal anterior pituitary glands. The pituitary stalk is normal and the posterior pituitary is not ectopic. Patients with *PROPI* mutations have been reported to show striking enlargement of the anterior pituitary, with suprasellar extension. The anterior pituitary may, in turn, become cystic leaving a near empty sella.

Conclusions

GHD may present at birth, usually if there are symptoms other than growth failure, because although children may be short at birth, their lengths are usually within normal limits. Post-natal growth failure may occur early in the months after birth, but in those with a hypothalamic

cause of GHD, growth may be preserved. GH levels should be assessed in any baby with severe or symptomatic hypoglycaemia in whom another cause is not obvious. IGF-I and IGFBP levels in infants and babies with suspected GHD should be compared with the normative data for their age.

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